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Selenium dioxide-mediated methoxyhydroxylation of cyclic arylolefin

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ABSTRACT

Selenium dioxide-mediated methoxyhydroxylation of cyclic arylolefin with the modest yields is described. This facile strategy was also used to synthesize several 4-arylpyridines, 3-hydroxy-4-arylpyridines, and 3,4-diarylpyridines.

1. Introduction

The contrasting chemical behaviors of 4-aryl-1,2,3,6-tetrahydropyridines are of interest.[1] Because the structural skeleton is known as a building partner in the synthesis of related compounds with potential pharmaceutical activities, our previous study developed a number of convenient procedures which allow the preparation of coerulescine and baclofen via a pinacol to pinacolone rearrangement reaction.[2] As part of an ongoing investigation in this area, we have developed the useful transformations that exploit the unique reactivity of the peroxyselenous ester derived from selenium dioxide and hydrogen peroxide in methanol to cyclic arylolefins.

In general, selenium dioxide displays an important mode of interaction with olefins, involving an initial ene reaction followed by a [2,3]-sigmatropic rearrangement.[3] The utility of this reagent as a selective allylic oxidant has been amplified by the addition of co-oxidant hydrogen peroxide which effectively prevents interference. Other selenium dioxide-catalyzed oxidative rearrangement reactions have also been reported.[4] One of the simplest ways of preparing α-methoxy alcohol is selective O-methylation of 1,2-diol, which can be easily done by dihydroxylation. Many reports on selective protection focus on the hydroxyl group of diol or ring-opening of epoxide by nucleophilic attack of alcohols. Under the condition of their experiments, the major problems involve the difficulty in selective protection of 1,2-diol or ring-opening of epoxide ring.

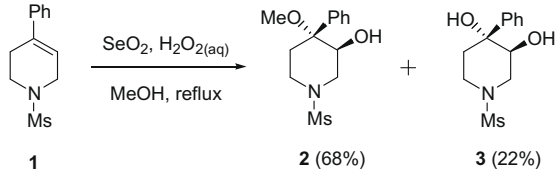
2. Results and discussion

To initiate our work, oxidation of olefin **1** (1.0 mmol) with selenium dioxide (2.0 equiv) and hydrogen peroxide (2 mL) in methanol (20 mL) at reflux temperature for 5 h provided methoxyalcohol **2** at a 68% yield and diol **3** at a 22% yield (Eq. 1).

The structure of methoxyalcohol **2** with trans-configuration was determined by single-crystal X-ray analysis (see Diagram 1). We have confirmed that water from aqueous hydrogen peroxide assisted the formation of diol **3**. Furthermore, by adjusting the solvent of hydrogen peroxide as the methanol[5] or dioxane, the yields of methoxyalcohol **2** (93%) or diol **3** (84%) were increased. To our knowledge, there is currently no experimental report on the selenium dioxide-mediated methoxyhydroxylation and dihydroxylation.

The possible methoxyhydroxylation reaction mechanism has been proposed as follows. Presumably, selenium dioxide exists as a form of peroxyselenous methylester in the hydrogen peroxide of methanol solution. When the epoxidation of olefin **1** is generated, it is assumed that the formation of the intermediate epoxide can be converted to methoxyalcohol **2** by means of a nucleophilic attack of epoxide with methanol with regio- and stereosensitivity. To further reinvestigate the reaction mechanism, two-step transformation was examined. Epoxidation of olefin **1** with *m*-chloroperoxybenzoic acid was tested. Then, treatment of the resulting epoxide with selenium dioxide (2.0 equiv) in methanol yielded methoxyalcohol **2**. The yield of two steps is 68%. Therefore, we believed that epoxidation is the first step during the selenium dioxide-mediated reaction. During the one-pot process, the *cis*-1,2-methoxyalcohol framework was not observed under this reaction condition.

When the amount of selenium dioxide was removed from the reaction system, we found that a nearly equivalent amount of olefin **1** was recovered. For the catalytic amount of selenium dioxide



1 **2** (68%) **3** (22%)

Equation 1. SeO_2-mediated reaction of olefin **1**.

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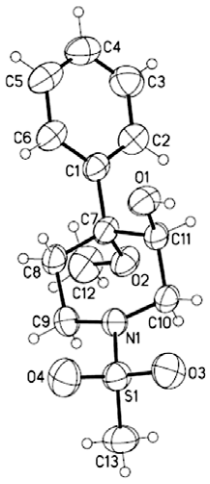


Diagram 1. X-ray structure of compound **2**.

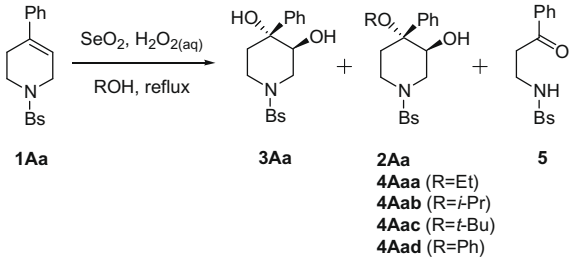
(0.3 equiv), the lower conversion was still generated. Olefin **1** was recycled in 66% yield. Furthermore, when selenium dioxide (1.3 equiv) was added to the reaction mixture, the products **2** (63%), **3** (20%), and trace olefin **1** were obtained during a 10-h period. In comparison with the amount of selenium dioxide, 2 equiv is the appropriate condition to shorten the reaction time. For screening other epoxidizing agent, we had tried to use *m*-chloroperoxybenzoic acid (2.0 equiv) instead of hydrogen peroxide in the selenium dioxide-mediated reaction of olefin **1**. We found that the residue mixture of *m*-chlorobenzoic acid and excess *m*-chloroperoxybenzoic acid was not easy to separate clearly from the product mixture by chromatography. The isolation procedure of products **2** and **3** was inconvenient than that of the oxidant hydrogen peroxide. To test the efficiency of the selenium dioxide-mediated reaction, several arylolefins were prepared to demonstrate the methoxyhydroxylation and dihydroxylation. As shown in Scheme 1, these starting six-membered materials included five 4-aryl-1,2,5,6-tetrahydropyridines **1Aa**–**1Ae** (a, Ar = Ph; b, Ar = 4-FPh; c, Ar = 3-CF_3Ph; d, Ar = 2-MeOPh; e, Ar = 3-CF_3-4-ClPh), 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyran **1B**, and 4-methyl-1-(4-fluorophenyl)-1-cyclohexene **1C**.

With compounds **1Aa**–**1Ac** and **1B**–**1C** in hand, two reaction conditions were examined. Skeleton **1** was subjected to oxidation using selenium dioxide and hydrogen peroxide in methanol or dioxane at reflux temperature. As revealed by TLC analysis, the starting materials disappeared with the appearance of a major product during a 5-h period. Isolation of the product after aqueous workup and characterization indicated the structural skeletons **2** and **3**. The isolated yields of products **2Aa**–**2Ae** and **2B**–**2C** were

Table 1
SeO_2-mediated reaction of **1Aa** with H_2O_2 in alcohols[a]

Entry	ROH (20 mL)	Time (h)	Yields[b] (%)
1	Methanol	5	**3Aa**/**2Aa**/**5**=61/24/ND
2	Methanol	25	**3Aa**/**2Aa**/**5**=16/30/37
3	Ethanol	5	**3Aa**/**4Aaa**/**5**=39/40/ND
4	Ethanol	25	**3Aa**/**4Aaa**/**5**=8/20/50
5	Isopropanol	5	**3Aa**/**4Aab**/**5**=26/32/ND
6	Isopropanol	25	**3Aa**/**4Aab**/**5**=5/14/40
7	*t*-Butanol	5	**3Aa**/**4Aac**/**5**=52/ND/ND
8	*t*-Butanol	25	**3Aa**/**4Aac**/**5**=trace/ND/48
9	Phenol	5	**3Aa**/**4Aad**/**5**=31/ND/ND

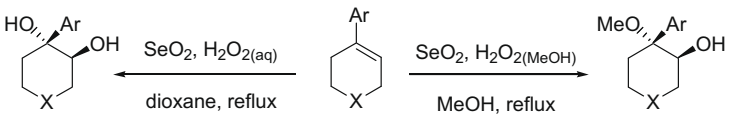
[a] The reactions were run on 1 mmol scale with alcohol at reflux temperature using selenium dioxide (2 equiv) and aqueous hydrogen peroxide (2 mL).
[b] ND is no detected product.



Equation 2. SeO_2-mediated reaction of olefin **1Aa** with alcohols.

in the 78–89% range and those of products **3Aa**–**3Ac** were in the 72–82% range.[6] We had tried to study the synthesis of five-membered 3-phenylpyrroline using the same treatment, but the attempt was unsuccessful. Although the synthetic application has been decreased, the present work is complementary to existing methodology. After many trials, different alcohol solvents were explored next.

As shown in Table 1 and Eq. 2, several alcohols were investigated to determine the reaction of olefin **1Aa** in the presence of water. For methanol, products **3Aa** and **2Aa** were obtained in 61% and 24% yields (entry 1). The result is similar to Eq. 1. In particular, a part of diol **3Aa** was converted to aminoketone **5** due to overoxidation under longer time conditions (entry 2). For ethanol, products **3Aa** and **4Aaa** provided 39% and 40% yields (entry 3), respectively. The ratio of alkoxyalcohol/diol (from 2.5 to 1) was decreased. A part of diol **3Aa** was also converted to aminoketone **5** (entry 4). In comparison with selenium dioxide-mediated alkoxyhydroxylation of olefin **1Aa** with methanol or ethanol, the poorer overall yields of products **3Aa** and **4Aab** showed that the steric effect of isopropanol controlled the distribution of products and yields (entry 5). Entry 6 also showed results similar to those of entry 4, but the overall yield

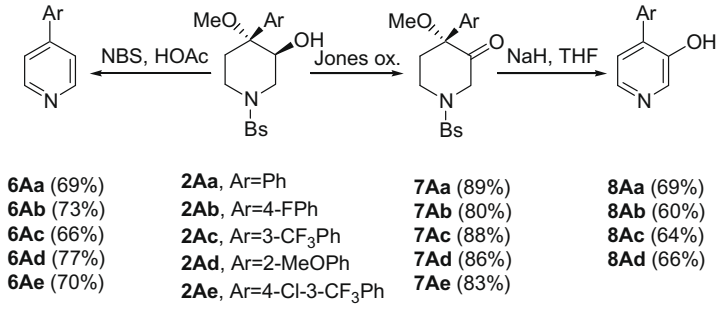


3Aa, X=NBs, Ar=Ph (82%)
3Ab, X=NBs, Ar=4-FPh (72%)
3Ac, X=NBs, Ar=3-CF_3Ph (75%)

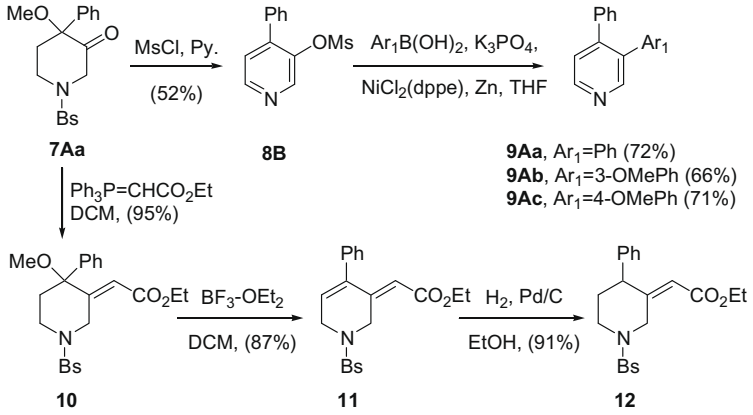
1Aa, X=NBs, Ar=Ph
1Ab, X=NBs, Ar=4-FPh
1Ac, X=NBs, Ar=3-CF_3Ph
1Ad, X=NBs, Ar=2-MeOPh
1Ae, X=NBs, Ar=3-CF_3-4-ClPh
1B, X=O, Ar=4-FPh
1C, X=CHMe, Ar=4-FPh

2Aa, X=NBs, Ar=Ph (89%)
2Ab, X=NBs, Ar=4-FPh (78%)
2Ac, X=NBs, Ar=3-CF_3Ph (85%)
2Ad, X=NBs, Ar=2-MeOPh (83%)
2Ae, X=NBs, Ar=3-CF_3-4-ClPh (88%)
2B, X=O, Ar=4-FPh (85%)
2C, X=CHMe, Ar=4-FPh (79%)

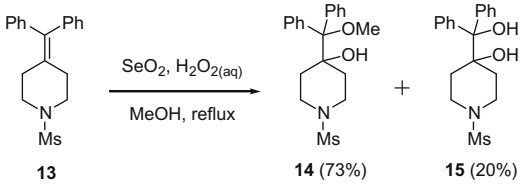
Scheme 1. SeO_2-mediated *trans*-methoxyhydroxylation and dihydroxylation of olefin **1**.



Scheme 2. Synthesis of 4-arylpyridines **6Aa–6Ae** and 3-hydroxy-4-arylpyridines **8Aa–8Ad**.



Scheme 3. Synthesis of 3,4-diarylpyridines **9Aa–9Ac** and compound **12**.



Equation 3. SeO_2-mediated reaction of olefin **13**.

is poorer. By changing isopropanol to *t*-butanol, diol **3Aa** was obtained as the major product in a 52% yield during a 5-h reaction time (entry 7). The product **5** was still generated with a 48% yield as a nearly sole isomer (entry 8). This is a new approach to the synthesis of β-aminoarylketone[7] via selenium dioxide-mediated oxidative bond cleavage with *t*-butanol. The evidence demonstrated that the steric hindrance was a key factor for the introduction of alcohol into the quaternary center. Reaction time was another factor in determining the bond cleavage of olefin. As shown in entry 9, because the nucleophilic ability of phenol was poorer than that of water, diol **3Aa** gave only a 31% yield. Similar results were obtained with the additive ethylene glycol.

To reinvestigate the applicability of the facile methoxyhydroxylation reaction, we studied the synthesis of substituted pyridine analogs, including 4-arylpyridines, 3-hydroxy-4-arylpyridines, and 3,4-diarylpyridines. 4-Arylpyridines are of high interest in organic chemistry due to their potential agrochemical and pharmaceutical activities and several synthetic procedures have appeared during recent years.[8] After screening numerous conditions, treatment of **2Aa** with *N*-bromosuccinimide in acetic acid at reflux temperature produced the desired 4-arylpyridine **6Aa** at a 69% yield as shown in Scheme 2. Similarly, the reaction of methoxyalcohols **2Ab**∼**2Ae** also furnished the resulting 4-arylpyridines **6Ab–6Ae** with 66–77% yields.

We next turned our attention to the synthesis of 3-hydroxypyridine. 3-Hydroxypyridines are important structural units found in numerous bioactive compounds.[9] Oxidation of alcohols **2Aa–2Ad** with Jones reagent in acetone at room temperature resulted in the corresponding ketones **7Aa–7Ad** being produced with 80–89% yields. The structure of ketone **7Aa** was determined by single-crystal X-ray analysis.[10] Based on the experimental simplicity, the preparation of ketone **7Aa** was also conducted in a multigram scale (0.1 mol) with a 75% overall yield. Treatment of ketones **7Aa–7Ad** with sodium hydride in tetrahydrofuran at reflux temperature produced 3-hydroxypyridines **8Aa–8Ad** in 60–69% yields. Compound **8Aa** is the key precursor in the synthesis of 3-phenyltropane analogs with some potent activities by 1,3-dipolar cycloaddition.[11] Furthermore, synthesis of diarylpyridines was described as follows. The aromatization process was also achieved via the reaction of ketone **7Aa** with methanesulfonyl chloride in pyridine at reflux temperature and mesylate **8B** provided a 52% yield as shown in Scheme 3. For introducing the 3-aryl group, Percec's coupling protocol was examined.[12]

Nickel complex-catalyzed Suzuki coupling of mesylate **8B** with three kinds of phenylboronic acid analogs gave diarylpyridines **9Aa–9Ac** in 66–72% yields. On the other hand, when compound **7Aa** was reacted with Wittig reagent, the sole olefin **10** was obtained in a 95% yield. Also, conjugated diene **11** was isolated by dehydration of compound **10** with boron trifluoride etherate at reflux temperature with a 87% yield. Selective hydrogenation of **11** produced **12** at a 91% yield. Noteworthy, unsaturated esters **11** and **12** were the piperidine-based analogs of cocaine.[13]

Finally, we examined an extension of the above-mentioned method to the synthesis of methoxyalcohol **14** and diol **15** (Eq. 3). The selenium dioxide-mediated reaction of exocyclic arylolefin **13** under the above-mentioned condition successfully furnished the *trans*-methoxyhydroxylation and dihydroxylation reactions. The structures of methoxyalcohol **14** and diol **15** were determined by single-crystal X-ray analysis.[14]

3. Conclusion

In summary, we have presented a synthetic method for 4-arylpyridines, 3-hydroxy-4-arylpyridines, and 3,4-diarylpyridines which involved selenium dioxide-mediated methoxyhydroxylation of 4-aryl-1,2,3,6-tetrahydropyridines. Considering the utility of these heterocyclic aromatic compounds, the development of the general synthetic approaches is significant.

Acknowledgment

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5. A solution of hydrogen peroxide in methanol is prepared from sodium peroxide. Sodium peroxide is added to an ice-cold dilute solution of 20% sulfuric acid in methanol, in small doses at a time. Sodium sulfate is removed by recrystallization, and a dilute solution of hydrogen peroxide in methanol is obtained. The concentration of the freshly prepared solution of hydrogen peroxide in methanol was nearly 38–42% (v/v) by titrating with the solution of potassium permanganate (0.02 M).
6. Selenium dioxide-mediated reaction of compound **1** into compounds **2** or **3** is as follows: A solution of hydrogen peroxide (2 mL) in methanol or water was added dropwise to a solution of compound **1** (1.0 mmol) with selenium dioxide (222 mg, 2.0 mmol) in methanol or dioxane (20 mL) at rt. The reaction mixture was stirred at reflux for 5 h. Saturated sodium bicarbonate solution (2 mL) was added to the reaction mixture and the solvent was concentrated. The residue was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to afford crude product. Purification on silica gel (hexane/AcOEt = 6/1–2/1) afforded compounds **2** and **3**. For compound **2Aa**: Mp= 137–138 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3519, 2940, 1338, 1168, 1123, 576 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{18}H_{22}NO_4S$ 348.1270, found 348.1271; ^1H NMR (400 MHz): δ 7.84–7.81 (m, 2H), 7.66–7.48 (m, 8H), 3.84–3.74 (m, 3H), 3.10 (dd, J = 2.8, 13.2 Hz, 1H), 2.84 (s, 3H), 2.66–2.52 (m, 2H), 2.12 (br s, 1H), 2.08 (br d, J = 14.8 Hz, 1H); ^{13}C NMR (100 MHz): δ 142.06, 136.45, 132.95 (2×), 130.47, 129.18 (2×), 128.98, 127.55 (2×), 124.77, 123.72, 77.17, 71.05, 49.67, 48.12, 41.46, 24.27; Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.38; H, 6.21; N, 4.33. For compound **3Aa**: Mp= 177–178 °C (recrystallized from hexane and ethyl acetate); IR ($CHCl_3$) 3489, 2921, 1336, 1169, 1078, 729 cm^{-1}; HRMS (ESI, M^++1) calcd for $C_{17}H_{20}NO_4S$ 334.1113, found 334.1113; ^1H NMR (400 MHz): δ 7.82–7.78 (m, 3H), 7.70–7.49 (m, 7H), 3.85–3.74 (m, 3H), 3.11 (dd, J = 1.2, 12.0 Hz, 1H), 2.85 (ddd, J = 2.4, 11.6, 12.8 Hz, 1H), 2.74 (ddd, J = 4.4, 12.8, 13.6 Hz, 1H), 1.74 (br d, J = 13.6 Hz, 1H), 1.68 (br s, 2H); ^{13}C NMR (100 MHz): δ 145.53, 136.28, 133.06 (2×), 129.39, 129.23 (2×), 128.89, 127.59 (2×), 124.86, 122.66, 72.11, 70.57, 48.36, 41.79, 31.41; Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.31; H, 5.83; N, 4.41.
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10. CCDC 752928 (**2**), 752931 (**3Ac**), 752932 (**4Aab**) and 752933 (**7Aa**) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
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14. CCDC 752929 (**15**) and 752930 (**14**) contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).